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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 10/084,676	Confirmation No.	: 2539
First Named Inventor	: Iris ZIEGLER		
Filed	: February 28, 2002		
TC/A.U.	: 1618		
Examiner	: Blessing Fubara		
Docket No.	: 029310.50932		
Customer No.	: 23911		
Title	: Oral Pharmaceutical Forms of Administration with a Delayed Action		

DECLARATION OF IRIS ZIEGLER UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Iris Ziegler, hereby declare as follows:

1. I am a citizen of the Federal Republic of Germany residing at Im Dickenbruch 4, D-52159, Roetgen, Germany.

2. I studied pharmacy at the University of Munich and received PhD degree in pharmaceutical technology in the year 1996.

3. Since 1996 I have been employed as a research pharmacist in the field of pharmaceutical technology, and I have been employed in this field by Gruenenthal GmbH of Aachen, Germany since 1997.

4. I am one of the inventors of the invention disclosed and claimed in the above-identified United States patent application no. 10/084,676, and I make this Declaration in support of said patent application.

5. The following tests were carried out in the Laboratories of Gruenenthal GmbH under my supervision and direction.

I(a). Preparation of Tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride according to US 5,914,129.

Tablets having the following composition were prepared by direct compression:

Composition	Amount
Diclofenac-sodium	50.0 mg
Tramadol-hydrochloride	75.0 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC591, FMC)	37.5 mg
Lactose monohydrate	50.0 mg
Crospovidone (Kollidon CLM, BASF)	22.5 mg
Microcrystalline cellulose & lactose monohydrate (Cellactose, Meggle)	256.0 mg
Magnesium stearate	1.4 mg
Total weight	529.9 mg

In order to produce the tablets, the Diclofenac-sodium, Tramadol-hydrochloride and the other substances listed above were screened through a 0.6 mm screen and then mixed for 10 minutes in a blender. The resulting blended mixture was compressed on a Korsch EK0 tablet press having a 15 x 6 mm die into oblong tablets each weighing 529.9 mg. The resulting tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride had a hardness of approximately 100N, and the disintegration time of the tablets was 5 minutes.

I(b) Preparation of Tablets containing an *in situ* Compound of Diclofenac-sodium and Tramadol-hydrochloride according to Application no. 10/084,676.

(i) Pellets containing an *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride were prepared from the following composition:

Composition	Amount
Diclofenac-sodium	50.0 mg
Tramadol-hydrochloride	75.0 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC591, FMC)	37.5 mg
Lactose monohydrate	50.0 mg
Total weight	250.0 mg

In order to produce the *in situ* compound, the Diclofenac-sodium, Tramadol-hydrochloride and the other substances listed above were homogeneously mixed in a Kenwood Chef mixer for 10 minutes and then granulated with water in an amount sufficient for moistening. The resulting sticky, lumpy mass of granules was then extruded in a Nica Type E140 extruder with a 1.0 mm extrusion die. The rods of extrudate were initially extremely sticky but changed in the course of the extrusion process to a very dry extrudate with insufficient plasticity for subsequent spheronization. The extrudate was moistened and granulated again, and the resulting granules were extruded again in the Nica extruder. The moist extrudate was then converted to round pellets of uniform size in a Nica Type S450 spheronizer. The round pellets were dried in a drying cabinet at a temperature of approximately 50°C and then fractionated into sieve fractions.

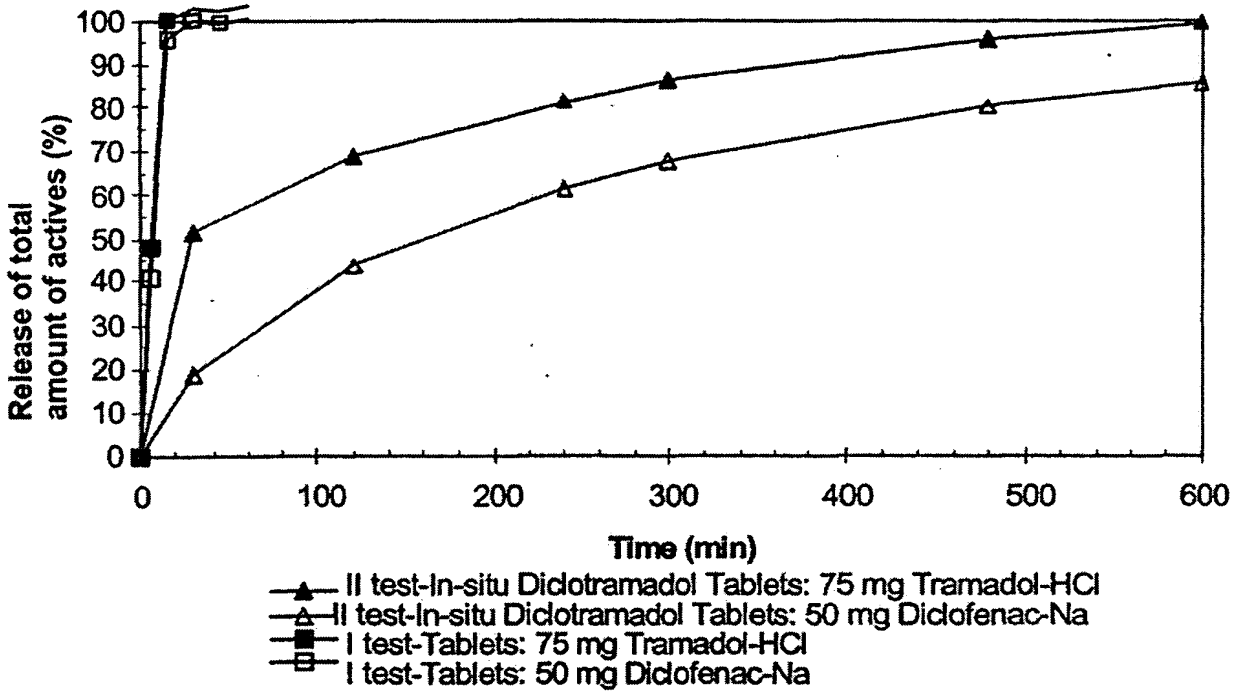
(ii) Tablets having the following composition were then prepared by direct compression:

Composition	Amount
Pellets from step (i) above containing *in situ* compound	250.0 mg
Crospovidone (Kollidon CLM, BASF)	22.5 mg
Microcrystalline cellulose & lactose monohydrate (Cellactose, Meggle)	256.0 mg
Magnesium stearate	1.4 mg
Total weight	529.9 mg

In order to produce the tablets, 250 mg of a 0.63 – 0.8 μm sieve fraction of the pellets from step (i) and the other ingredients listed above were compressed on a Korsch EK0 tablet press having a 15 x 6 mm die into oblong tablets each weighing 529.9 mg. The resulting tablets containing the *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride had a hardness of 60 – 80N, and the disintegration time of the tablets was less than 5 minutes.

I(c) Determination of Active Ingredient Release Profiles

The release profiles of Diclofenac and Tramadol from the tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride obtained in I(a) and the tablets containing an *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride obtained in I(b) above were determined by HPLC as described on page 11 of application no. 10/084,676 in 900 ml of simulated intestinal fluid (pH 7.2) at a rotational speed of 50 rpm. The results are shown in the following graph:



I(d) Discussion

Notwithstanding the fact that the tablets of I(a) and I(b) were identical in size and shape and were made from identical amounts of the same raw ingredients and differed only in their manner of processing, the tablets of I(a) which contained a mixture of Diclofenac-sodium and Tramadol-hydrochloride exhibited a significantly different release profile of both active substances than the tablets of I(b) which contained the *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride. The tablets of I(a) which contained a mixture of Diclofenac-sodium and Tramadol-hydrochloride exhibited a fast release of 100% of both active ingredients within approximately 15 minutes. In contrast thereto, 600 minutes were required to release 100% of the Tramadol and approximately 85% of the Diclofenac from the tablets of I(b) containing the inventive, *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride. The fact that the tablets of I(a) and I(b) exhibited similar hardness and disintegration

times shows that the slower release from I(b) is not attributable to different physical characteristics of the tablets. Rather, the slower release profiles from the tablets of I(b) demonstrate that the Diclofenac and Tramadol in the tablets of I(b) are present in a physical/chemical form (i.e., a lower solubility compound) which is clearly different from the mixture contained in the tablets of I(a).

6. The existence of an *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride in the tablets of I(b) produced according to the present invention is further demonstrated by Differential Scanning Calorimetry (DSC) thermal analyses which were carried out according to my directions. All DSC thermal analyses were performed in the Analytical Chemistry Department of Gruenenthal GmbH using the following parameters:

- using a 40 µl crucible with a perforated cap;
- heating from 30.0°C to 320°C at a rate of 10°C per minute, and;
- flushing with nitrogen gas at 50 ml per minute.

The results of each differential scanning calorimetry scan were plotted with a chart recorder such that endothermic events, such as the melting of individual constituents of the test substances, were indicated by upwardly directed peaks on each plot.

II(a) Tablets obtained in I(a) above containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride were crushed and subjected to DSC as described above. The results are shown in the diagram attached as **Exhibit A.**

II(b) Pellets obtained in I(b)(i) above containing the *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride were also crushed and subjected to DSC as described above. The results are shown in the diagram attached as **Exhibit B.**

II(c) Since Diclofenac-sodium and Tramadol-hydrochloride can react to form a salt of Tramadol and Diclofenac, a further test was carried out to demonstrate that the *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride was not the salt of Tramadol and Diclofenac.

(i) The salt of Tramadol and Diclofenac was prepared by dissolving equimolar amounts of Tramadol-hydrochloride and Diclofenac-sodium in separate water solutions. The two solutions were then mixed together under stirring and then cooled to precipitate the salt of Tramadol and Diclofenac, which was isolated and purified with ethanol by conventional methods.

(ii) The recovered and purified salt was then formulated into pellets having the following composition:

Composition	Amount
Salt of Tramadol and Diclofenac	125.0 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC591, FMC)	37.5 mg
Lactose monohydrate	50.0 mg
Total weight	250.0 mg

as described in I(b)(i) above, except that the wet mass was only granulated and extruded once prior to spheronization.

(iii) Pellets obtained in II(c)(ii) above containing the salt of Tramadol and Diclofenac were also crushed and subjected to DSC as described above. The results are shown in the diagram attached as **Exhibit C**.

II(d) To demonstrate that the difference between the DSC analysis of the pellets of I(b)(i) containing the *in situ* formed compound of Diclofenac-sodium and

Tramadol-hydrochloride and the pellets of II(c)(ii) containing the salt of Tramadol and Diclofenac was not caused by the presence of sodium chloride (NaCl), 500 mg of the crushed pellets of II(c)(ii) containing the salt of Tramadol and Diclofenac were admixed with 26.25 mg of NaCl, and the resulting mixture was subjected to DSC as described above. The results are shown in the diagram attached as **Exhibit D**.

II(e) To exclude the possibility that the results of the DSC analysis were influenced by the tabletting process of I(a), a sample of the blended mixture prior to tabletting was also subjected to DSC analysis. The results are shown in the diagram attached as **Exhibit E**.

II(f) Discussion

By comparing the two scans of **Exhibits A and B** the existence of a pronounced peak in **Exhibit B** at approximately 292°C, which has no counterpart in the scan of **Exhibit A** is evident. This peak shows the presence of a chemical entity in the pellets of I(b)(i) produced according to the present invention which is not present in the tablets of I(a) produced according to the teachings of Mauskop, US 5,914,129.

The difference between the scans of **Exhibits B and C** indicates that the product of the present invention is not the salt of Tramadol and Diclofenac since that pronounced peak in **Exhibit B** at approximately 292°C is missing in **Exhibit C**.

The essential similarity between the scan of **Exhibit C**, which shows the DSC analysis of the salt of Tramadol and Diclofenac, and the scan of **Exhibit D**, in which sodium chloride is added, establishes that the difference between the scans of **Exhibits B and C** is not attributable to the presence of sodium chloride which may form during the process.

Finally, the essential similarity between the scan of **Exhibit A**, which shows the result of a DSC scan of a tablet containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride, and the scan of **Exhibit E**, which shows the result of a

scan of a blended powder mixture containing Diclofenac-sodium and Tramadol-hydrochloride, establishes that the tabletting process does not change the DSC results.

7. The different release profiles of the Tramadol and Diclofenac from the tablets of I(b) produced according to the present invention compared to the tablets of I(a) produced according to the teachings of Mauskop, US 5,914,129 containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride, are indicative of a significant difference in solubility and demonstrate that the Diclofenac and Tramadol must be present in a physical/chemical form which is different from a mixture as taught by Mauskop. The different differential scanning calorimetry results of the pellets of I(b)(i) produced according to the present invention compared to the tablets of I(a) containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride according the teachings of Mauskop, US 5,914,129, and particularly the endothermic peak at approximately 292°C which has no counterpart in the DSC of the crushed tablets of I(a), corroborate the presence of a different physical/chemical species in the product of the present invention which is not present in the tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride as taught by Mauskop. These results evidence that the product of the present invention contains an *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride which is not present in the tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride as taught by Mauskop.

8. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements

may jeopardize the validity of this patent application or any patent issued thereon.

Date: 14 Dec 2006

I. Ziegler

Iris Ziegler

DEC 15 2006
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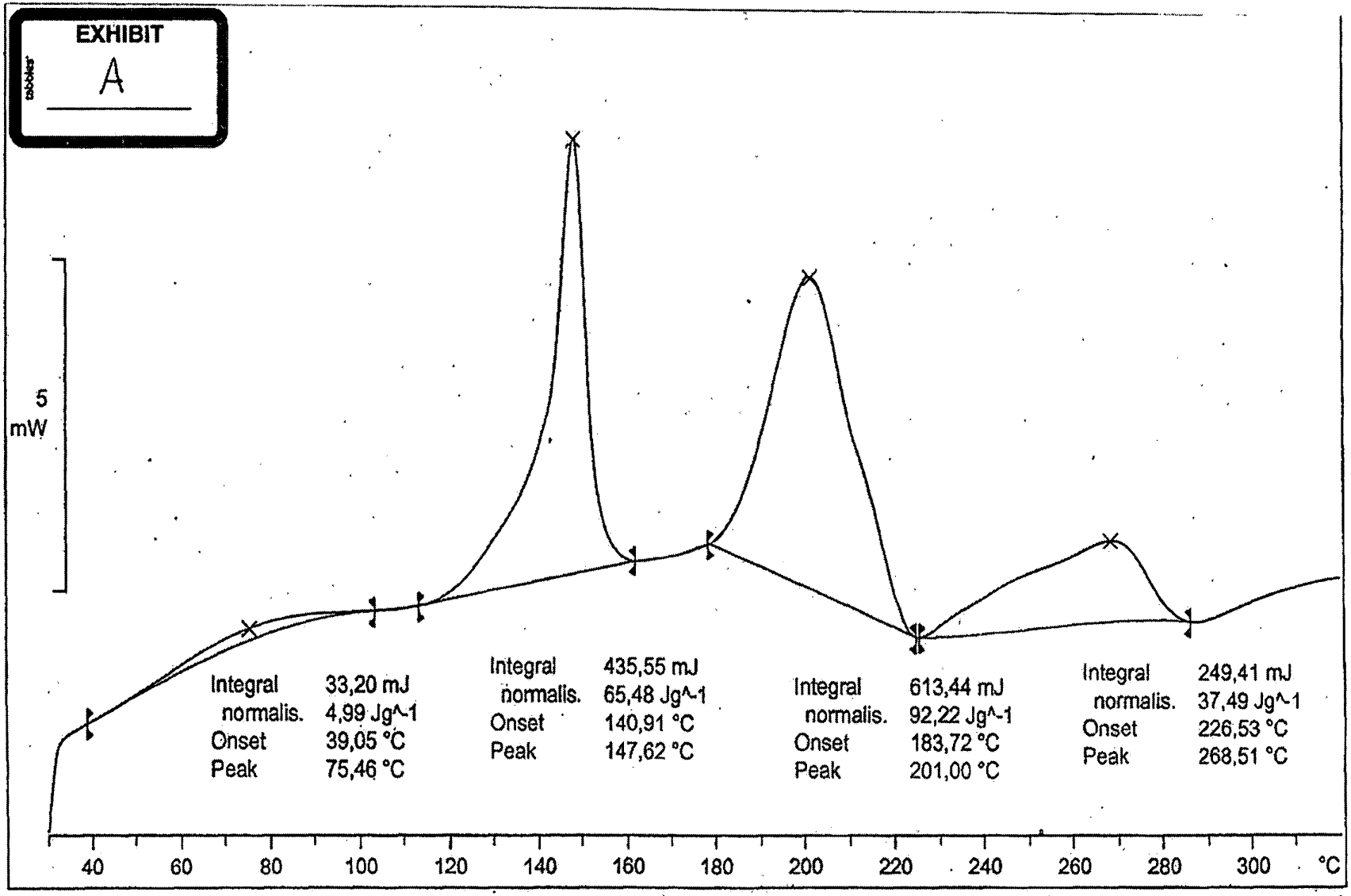
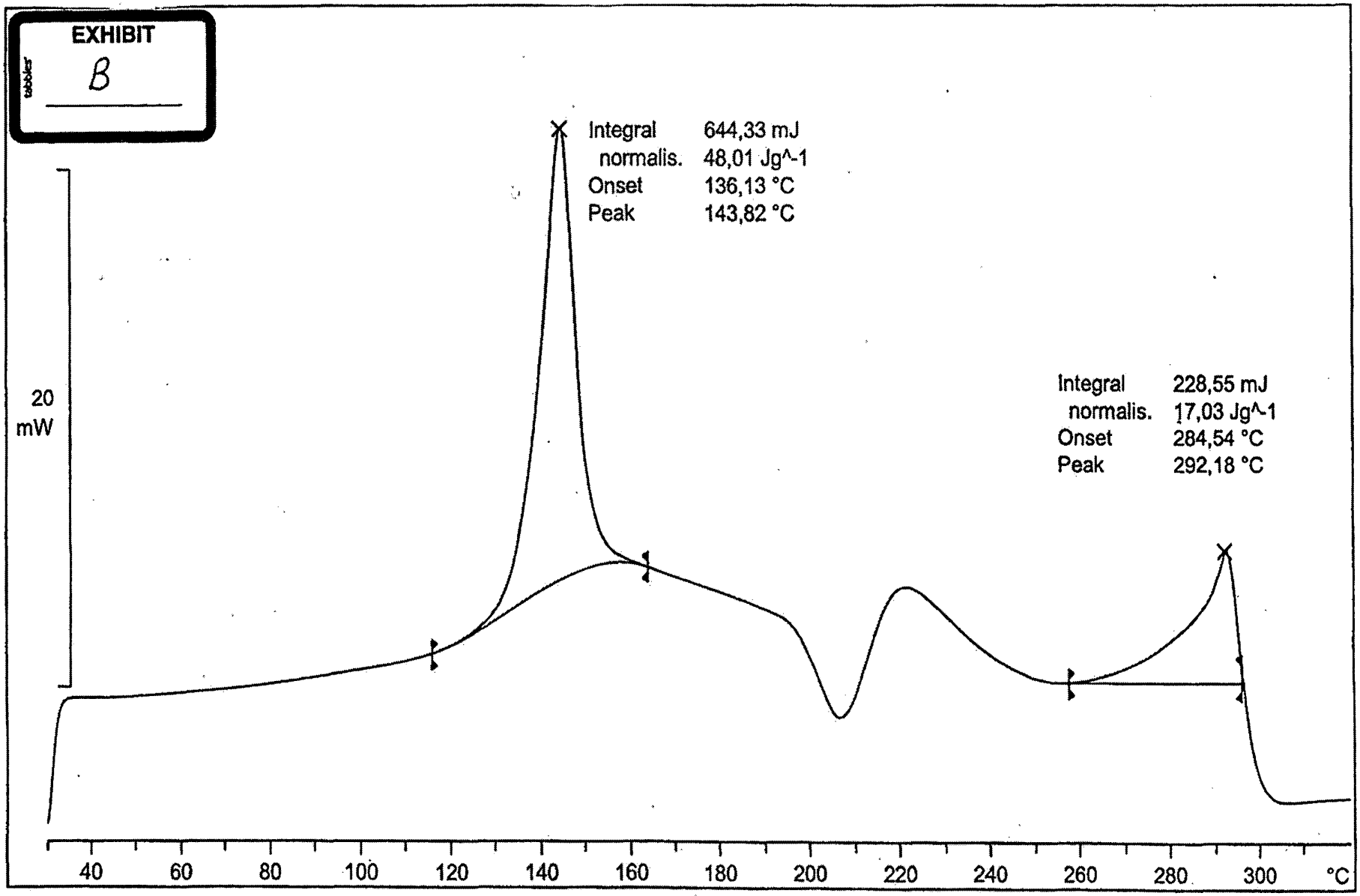
Crushed Tablets containing Blended Powder containing Tramadol-HCl and Diclofenac-Na

EXHIBIT
A

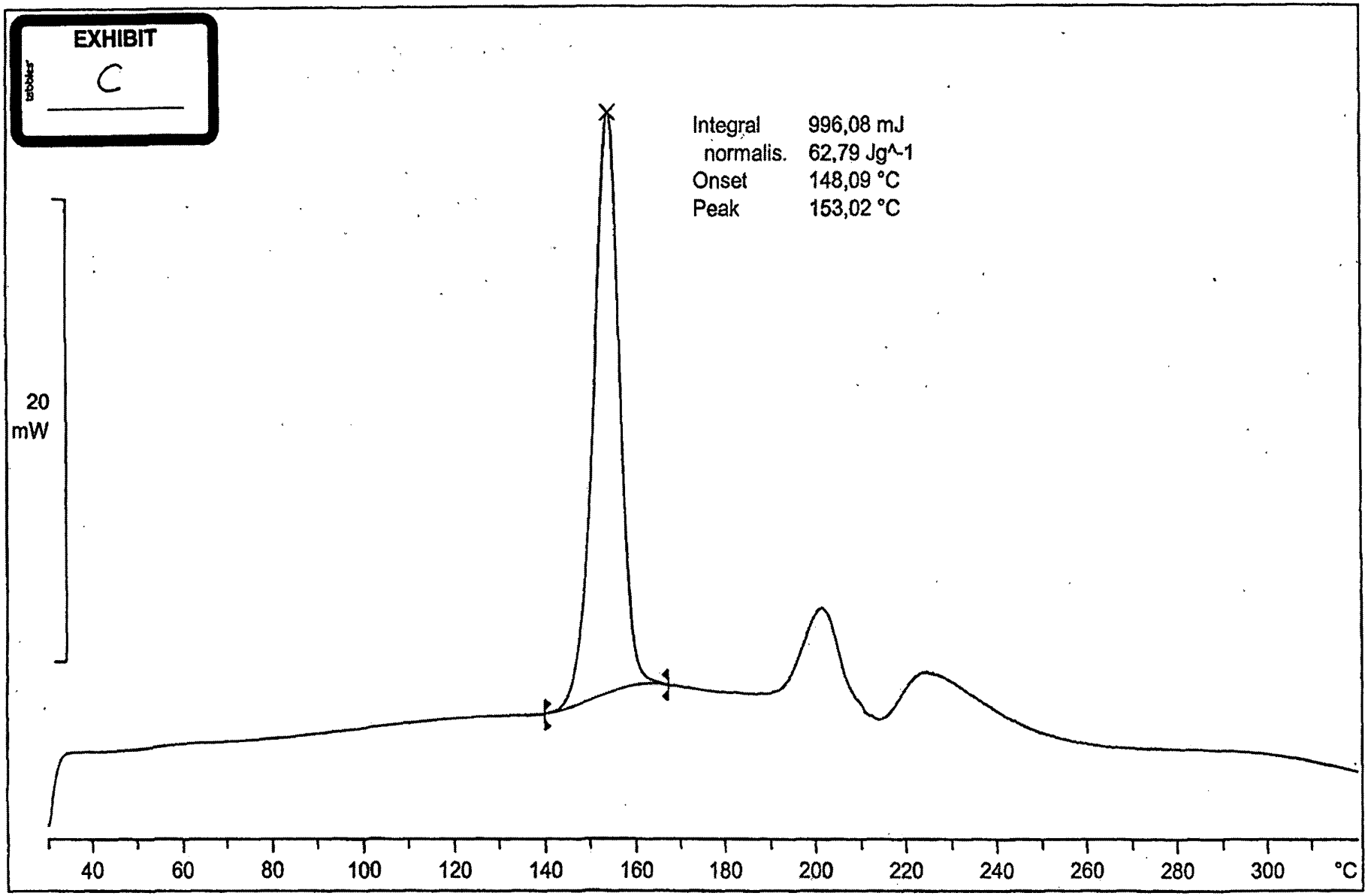


Crushed Pellets containing *in situ* formed Compound of Tramadol- HCl and Diclofenac-Na

EXHIBIT
B

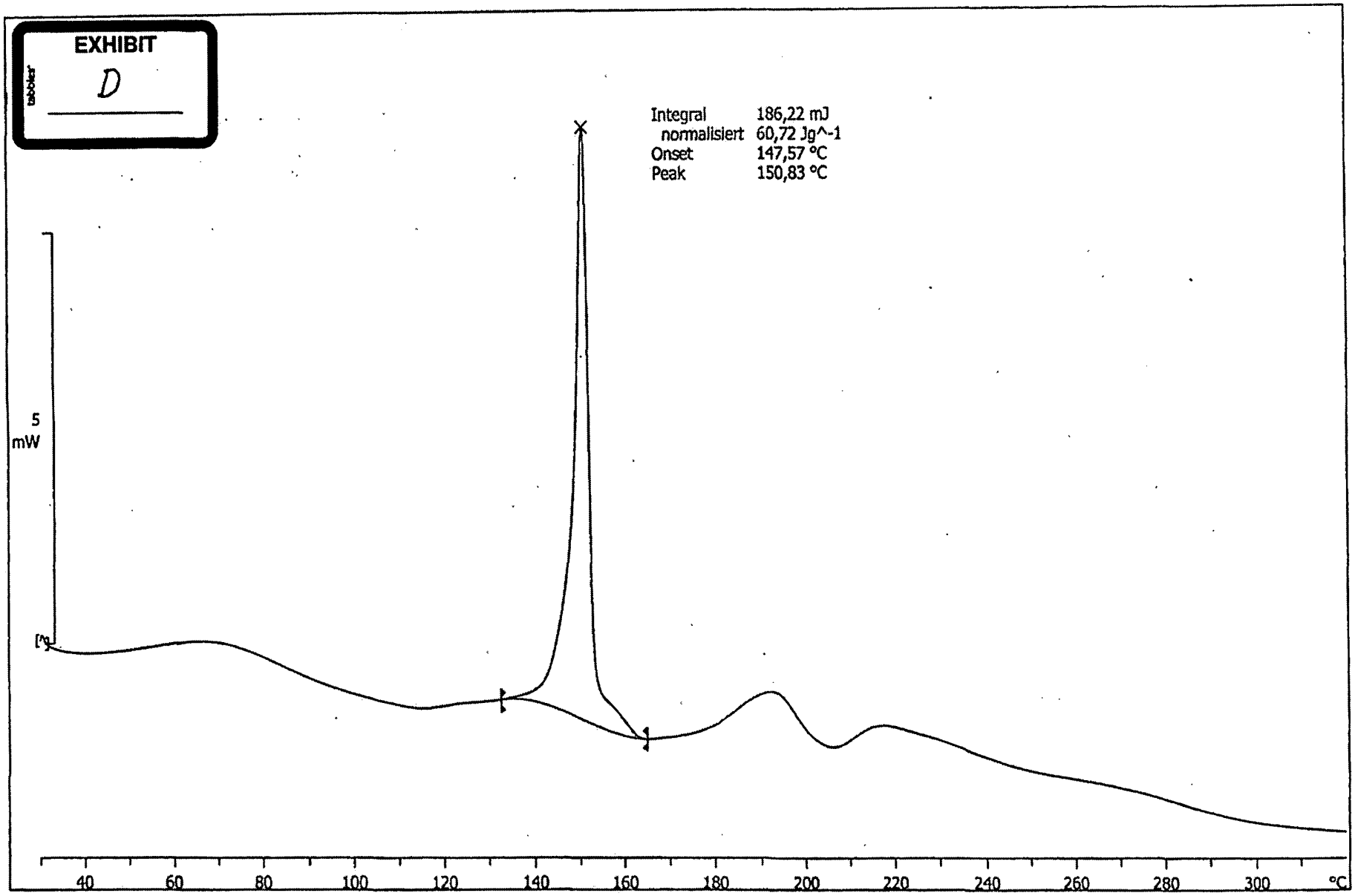


Crushed Pellets containing Salt of Tramadol and Diclofenac



Crushed Pellets containing Salt of Tramadol and Diclofenac and Added NaCl

EXHIBIT
D



Blended Powder containing Tramadol-HCl and Diclofenac-Na

EXHIBIT
E